

Form PTO 1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV 5-93)		ATTORNEY'S DOCKET NUMBER C75101
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/031143
INTERNATIONAL APPLICATION NO. PCT/US00/18896	INTERNATIONAL FILING DATE 12 July 2000	PRIORITY DATE CLAIMED 12 July 1999
TITLE OF INVENTION Heartburn Treatment		
APPLICANT(S) FOR DO/EO/US Kenneth G. MANDEL, Steven M. JOHNSON		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☒ Please amend the specification by inserting before the first line the sentence: This is a §371 national stage entry of International Application PCT/US00/18896, filed 12 July 2000, which claims benefit from the following Provisional Application: 60/143,407, filed 12 July 1999.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ An Abstract on a separate sheet of paper.
19. ☐ Other items or information:

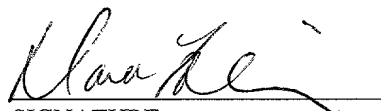
US APPLICATION NO. (if known see 37 CFR 1.50) 10/031143		INTERNATIONAL APPLICATION NO. PCT/US00/18896		ATTORNEYS DOCKET NO. C75101	
20. [X] The following fees are submitted:				CALCULATIONS PTO USE ONLY	
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):				\$710.00	
Search Report has been prepared by the EPO or JPO\$890.00					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492)\$710.00					
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2))\$740.00					
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....\$1,040.00					
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4).....\$100.00					
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$710.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$0.00	
Claims	Number Filed	Number Extra	Rate		
Total claims	10 - 20 =	0	0 x \$18.00	\$0.00	
Independent claims	1 - 3 =	0	0 x \$84.00	\$0.00	
Multiple dependent claims (if applicable)			+ \$280.00	\$710.00	
TOTAL OF ABOVE CALCULATIONS =				\$710.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$	
SUBTOTAL =				\$710.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				\$	
TOTAL NATIONAL FEE =				\$710.00	
				Amount to be refunded	\$
				charged	\$710.00

- a. ☐ A check in the amount of \$_____ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **\$710.00** to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570. A duplicate copy of this sheet is enclosed.
- d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE
Dara L. Dinner
NAME
33,680
REGISTRATION NO.

PATENT
ATTORNEY'S DOCKET NUMBER C75101

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE
(DO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/18896	12 July 2000	12 July 1999

TITLE OF INVENTION
Heartburn Treatment

APPLICANT(S) FOR DO/US
Kenneth G. MANDEL, Steven M. JOHNSON

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231
ATTENTION: DO/US

PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to calculation of the filing fees and examination of the above noted application, entrance of the following remarks and amendments into the record is respectfully requested.

In the Claims:

Please amend the following claims:

5. (Amended) The method according to Claim 1 wherein the bicarbonate is sodium or potassium bicarbonate or a mixture thereof.

REMARKS


This Preliminary Amendment is being made upon entry of International Application No. PCT/US00/18896 in the U.S. §371 national phase of prosecution. Claim 5 has been amended to remove multiple dependency and to conform to US Practice. Claims 1 to 12 are in the application.

A marked version of the amended claims accompanies this paper.

An abstract on a separate sheet of paper accompanies this request.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



Dara L. Dinner
Attorney for Applicant
Registration No. 33,680

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10/031143

MARKED UP VERSION OF CLAIMS TO SHOW CHANGES MADE

3. (Amended) The method according to [any one of Claims 1 to 4] Claim 1 wherein the bicarbonate is sodium or potassium bicarbonate or a mixture thereof.

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2433	2434	2435	2436	2437	2438	2439	2440	2441	2442	2
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ABSTRACT

The present invention is directed to the use of an alkali metal salt of a bicarbonate, preferably sodium bicarbonate, and an effective amount of a proton pump inhibitor in combination for the treatment of heartburn symptoms.

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HEARTBURN TREATMENT

FIELD OF THE INVENTION

This invention discloses use of an omeprazole-bicarbonate combination for the treatment of heartburn, and acid indigestion.

10

BACKGROUND OF THE INVENTION

US patent, 5,840,737, Phillips, J. issued Nov 24 1998, describes a combination of a bicarbonate salt and omeprazole. The claims are directed to treatment of gastric acid disorders (unspecified) with a single dose of a pharmaceutical composition of omeprazole or lansoprazole together with a bicarbonate salt (Na or K preferred). The dose is orally administered as an aqueous solution or suspension.

The Philips patent focuses on the prophylactic prevention of upper GI bleeding in critically ill patients. It is particularly directed toward stress ulcer prophylaxis which has become routine therapy in intensive care units in most hospitals. An inherent advantage is the ability to infuse the solution via a nasogastric tube directly into the stomach. Data indicates that the omeprazole-bicarbonate solution/suspension combine the rapid onset of pH neutralization (due to bicarbonate) with the prolonged duration of effect of the proton pump inhibitor (PPI). There is an enhancement in time to onset of action of the PPI, omeprazole. This is postulated to reflect an effect of the bicarbonate to enhance the absorption of omeprazole. Indeed, in the presence of the bicarbonate omeprazole is observed to more rapidly become available systemically, and initial absorption of omeprazole is observed within 10-12 minutes in the combination as compared to 2-3 hours for omeprazole administered as enteric coated pellets.

However, Phillips does not suggest that the administration of a PPI plus a bicarbonate would be useful as a means to provide rapid onset, and prolonged duration of effect for relief of heartburn symptoms, nor in avoiding the reoccurrence of heartburn symptoms.

Omeprazole has been formulated in many different embodiments such as in a mixture of polyethylene glycols as shown in U.S. Pat. No. 5,219,870 to Kim; U.S.

Pat No. 5,395,323 to Berglund discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient.

U.S. Pat. No. 4,786,505 to Lovgren et al., discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH.

The ability to provide a patient with a single dose administration of a preparation which has a rapid onset of acid neutralization would be a highly desirable dosage form for the treatment or prevention of heartburn symptoms.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating and/or preventing heartburn symptoms in a human in need thereof, which method comprises administering to said human a pharmaceutical composition comprising an effective amount of a proton pump inhibitor and an effective acid neutralizing amount of an alkali metal bicarbonate salt.

The administration preferably consists of a single dosage without requiring further administration of a second dose of a bicarbonate salt.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to single dose administration of a pharmaceutical composition for relief of heartburn symptoms. The term "heartburn symptoms" as used herein includes heartburn related to indigestion, sour stomach, upset stomach, episodic and co-incidental heartburn with meals, and heartburn related to gastroesophageal reflux of acid stomach contents. These are generally well recognized symptoms which are typically treated with, over-the-counter (OTC) medications, such as antacids, and more recently histamine H₂ receptor antagonists at reduced dosage. The treatments considered herein are the same as those symptoms for which various regulatory agencies, such as the FDA, have approved the use of H₂ receptor antagonists without prescription.

The present invention's use in the treatment of heartburn is a treatment which is safe, effective and useful for self-limiting gastrointestinal conditions. This

treatment is in contrast to the use of a proton pump inhibitor and an alkali metal bicarbonate salt for medically diagnosable gastrointestinal diseases, such as active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. The dosage administration is basically a once only treatment, and is not necessarily used for multiple daily dosing over a period of many days, weeks or long term duration, although it is recognized that it could be used as such.

Suitable proton pump inhibitors (PPI) useful in the present invention include those antisecretory compounds belonging to the class of compounds generally referred to as substituted benzimidazoles. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Also suitable for use herein are the individual enantiomers, of omeprazole, such as the (S) isomer, or a suitable salt form, such as the calcium or magnesium salts, or a combination of both such as the (S) magnesium salt of omeprazole. Other substituted benzimidazoles suitable for use herein include, but are not limited to lansoprazole, 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole; pantoprazole, 5-(Difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, and rabeprazole 2[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole.

This class of compounds (the proton pump inhibitors) inhibit gastric acid secretion and do not exhibit anti-cholinergic or histamine H₂ antagonist properties.

Drugs of this class suppress gastric acid secretion by the specific inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell.

Current use of proton pump inhibitors, particularly intravenous or oral liquid dosage forms is primarily directed towards medically diagnosable treatment of ulcers, or other medical determined mucosal bleeding of the gastrointestinal tract. Combinations of various H₂-antagonists, antacids and sucralfate are other currently used treatment options as prophylaxis for such damage.

These uses are however, not directed to the prevention or the treatment of heartburn symptoms.

Several buffered omeprazole solutions have been disclosed in publications, Andersson et al., Clinical Pharmacokinetics 24(1):71-8 (1993); Landahl et al. Clinical Pharmacokinetics 23 (6); 469-76 (1992); Andersson et al., Br. J. Clin. Pharmacol., 29(5):557-63 (1990); Regardh et al., Ther. Drug Monit. 12(2):163-72 (1990);

Andersson et al., *Eur. J. Clin. Pharmacol.*, 39(2):195-7 (1990); and Pilbrant et al., *Gastroenterol Suppl.*, 108:113-20 (1985).

All of the buffered omeprazole solutions described in these publications were administered orally and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration. In all of these studies, the repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration.

The bicarbonate was not given for its acid neutralizing capacity as an antacid, but for its use in preventing the degradation of the PPI. As a result, the ingestion of the large amounts of sodium bicarbonate and large volumes of water were required in contrast to the present invention. In these above-cited studies, as much as 48 millimoles of sodium bicarbonate in 300 ml of water were ingested in association with a a single dose of omeprazole for oral administration.

The present invention does not require the ingestion of excessive volumes of bicarbonate with water. Furthermore, the enhancement in onset of the PPI's action allows use of a minimal dose to achieve rapid and long-lasting relief of heartburn symptoms. The use of the combination of the PPI and bicarbonate permits using the PPI at dosages which are often suboptimal for standard Rx therapeutic applications (e.g., healing of duodenal or gastric ulcers, healing esophageal erosions, etc.). In the case of omeprazole, a dosage of about 10 to about 20 mg is desired.

Another aspect of the present invention is a dosage form of the omeprazole and bicarbonate which can be utilized to quickly make an omeprazole solution/suspension which is supplied in a solid form, such as in a powder form of a sachet, or as readily dispersible tablet or capsule. Alternatively the solid dosage form of omeprazole and bicarbonate, such as in a compressed tablet or capsule for oral ingestion may also be suitable, or even desired for use by the patient for the treatment of their heartburn symptoms.

An advantage of either the solution/suspension formulation or the solid dosage formulation are that both provide a means for the rapid onset and prolonged duration of effect for relief of heartburn symptoms and avoid the recurrence of these heartburn symptoms.

The pharmaceutical composition of the present invention may be prepared in accordance with Phillips, J., US Patent No. 5,840,737 whose disclosure is incorporated

herein by reference in its entirety. The composition may also be prepared by mixing omeprazole or other substituted benzimidazoles and derivatives thereof, with a solution including a bicarbonate salt of a Group IA metal. Preferably, omeprazole powder or granules, which may be enteric coated or not, are mixed with a sodium bicarbonate solution to achieve a desired final omeprazole concentration. The concentration of omeprazole in the solution/suspension can range from approximately 0.25 mg/ml to approximately 6.0 mg/ml. The preferred concentration for the omeprazole in the solution/suspension ranges from approximately 0.5 mg/ml to approximately 2 mg/ml.

The pharmaceutically acceptable alkali metal salt of a bicarbonate is preferably a Group IA metal salt, such as potassium or sodium. The concentration of the bicarbonate salt in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt ranges from approximately 7.5 percent to approximately 10.0 percent. In one embodiment of the present invention, sodium bicarbonate is the preferred salt and is present in a concentration of approximately 8.4 percent. A sufficient acid neutralizing capacity (ANC) amount is necessary and that will range from about 5 to about 40 ANC values, preferably from about 18 to 40 ANC values. It should be noted that the FDA considers an ANC value of 5 to be the minimum amount useful as an antacid. In the case of sodium or potassium bicarbonate preferred range is 18 to 40mEq, for calcium bicarbonate it is from about 36 to 80 mEq.

The amount of sodium bicarbonate used in the solution/suspension of the present invention is approximately 1 meq (or mmole) sodium bicarbonate per 1-2 mg omeprazole, with a range of approximately 0.75 meq (mmole) to 2.0 meq (mmole) per 1-2 mg of omeprazole, preferably 0.5 to 1.5mEq/1-2 mg of omeprazole.

In another aspect of the present invention, enterically-coated omeprazole granules may be used and admixed with the sodium or potassium bicarbonate (NaHCO_3) solution which dissolves the enteric coating and forms an omeprazole solution/suspension for use in accordance with the present invention. Alternatively a solid dosage formulation of the enteric coated granules with the bicarbonate may be made and placed into capsules, or using the many techniques now known in the art, formulated into a compressed tablet.

Alternatively, micronized granules of a PPI, such as omeprazole may be used in place of conventional granules or powder. The process known as micronization is utilized in order to produce a particle having a smaller diameter. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size

increases the surface area, reducing the particle size increases the dissolution rate. Although micronization results in increased surface area causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole.

The formulation may contain suitable flavoring agents for use herein including, but not limited to, wintergreen, orange, grapefruit, chocolate, and cherry-raspberry. The amount of flavouring present in the formulation may be from about 0.1% to about 5.0% by weight of the composition.

The solid formulations may optionally contain suitable disintegrants such as, but not limited to, sodium starch glycolate [Explotab®], crosslinked polyvinylpyrrolidone, corn starch, acacia, Croscarmellose of sodium [Ac-di-sol®], sodium carboxymethylcellulose, veegum, or alginates. The amount of disintegrant present may be from about 1% to about 10.0% by weight of the composition.

The formulation may also include additional diluents or fillers which are preferably swellable agents, and may include, but are not limited to, various grades of microcrystalline cellulose, such as Avicel PH101, Avicel PH102, & Avicel PH200; corn starch; or Starch 1500. The amount of diluent or filler present in the formulation may be from about 1% to about 90.0% by weight of the composition.

The dosage form may also optionally contain suitable lubricants or wetting agents, such as but not limited to, magnesium stearate, stearic acid and its pharmaceutically acceptable alkali metal salts, calcium stearate, sodium stearate, Cab-O-Sil, Syloid, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate or talc. Preferably, a suitable lubricant is magnesium stearate or stearic acid. Preferably, a suitable wetting agent is a surfactant, such as sodium lauryl sulfate. The amount of lubricant present in the formulation may be from about 0.1% to about 10.0% by weight of the composition, whereas the amount of wetting agent may be from about 0.1 – 20% by weight.

The formulation may also include additional binding agents, such as polyvinylpyrrolidone, (PVP), or Povidone 29K/32. The amount of binding agent present in the formulation may be from about 0.1% to about 30.0% by weight of the composition.

The formulation may also include coloring agents, or pigments, such as FD&C or D&C approved lakes and dyes, iron oxide and titanium dioxide. The amount of pigment present may be from about 0.1% to about 5.0% by weight of the composition.

Additional other conventional pharmaceutical diluents or excipients may also be included, as needed, in the admixture. Suitable excipients which may be employed include, for example, fillers, binders, lubricants, binders, compression aids, and wetting agents. To further assist patient compliance, the formulation may also

5 contain sweeteners such as various natural sugars, aspartame, sodium cyclamate and sodium saccharinate; in addition to the flavorants. The amount of sweetener present may be from about 0.1% to about 20.0% by weight of the composition.

The formulations may also be manufactured in a concentrated form, such as an effervescent tablet, for oral administration upon admixture with water. Suitable

10 effervescent formulations for use herein are well known in the art.

The following data illustrates the utility of the pharmaceutical composition of the present invention.

15 **Comparison of onset of acid inhibition between omeprazole alone and the omeprazole – bicarbonate combination.**

Khoury, *et al.* studied onset of acid inhibition following a single postprandial administration of omeprazole 10 or 20 mg in healthy volunteers. Khoury, et al., *Am. J. Gastroenterol.* 93: 1619, (1998). The effect of omeprazole was compared with

20 ranitidine, 75 and 150 mg. Gastric acid was measured via an intragastric pH probe. The design was a randomized crossover in 24 subjects. A standardized breakfast was consumed, drug was administered once intragastric pH returned to pH < 2.0, and intragastric pH recorded for 6 hr. Omeprazole, at both 10 and 20 mg failed to elevate intragastric pH to values ≥ 3.0 during the 6 hour postprandial recording

25 period. In contrast, ranitidine 75 mg and 150 mg elevated intragastric pH > 3.0 within 178 and 145.5 min of dosing, respectively, and sustained pH > 3.0 for 2 and 3 hours of the recording period. Hence in this study, a single postprandial dose of 10 or 20 mg omeprazole had no effect on intragastric acidity for 6 hours following administration in healthy individuals.

30 Similarly, Decktor, *et al.* compared effects of single administrations of omeprazole 10 or 20 mg, famotidine 10 mg and placebo on meal-stimulated gastric acid secretion. Decktor, et al., *Am. J. Gastroenterol.* 92: 1588, (1997). In a blinded, placebo-controlled cross-over study, each of 12 subjects randomly received the treatments one hour prior to intragastric infusion of a liquid peptone meal (600 ml

35 8% peptone, pH 4.0) designed to maximally stimulate acid output. Intragastric pH was maintained at pH 4.0 by continuous infusion of NaOH. Compared to placebo,

onset of significant acid antisecretory activity was observed 45 min, 75 min and 90 min following meal infusion for famotidine, omeprazole 20 mg and omeprazole 10 mg respectively. Over a 5 hr recording period, 10 mg famotidine reduced the amount of titrant required to maintain pH at 4.0 by 81%, while reductions of 56% and 27% were obtained with 20 mg and 10 mg omeprazole respectively. Famotidine 10 mg had a significantly faster onset of action and significantly greater antisecretory effect than omeprazole

The Phillips U.S. patent No. 5,840,737 in contrast, reports that single administration of bicarbonate + omeprazole elevates intragastric pH in critically ill patients from 3.0 ± 0.7 to 7.0 ± 0.6 within 2 hours after dosing. The dose was 20 mEq ANC provided by bicarbonate and a 40 mg omeprazole dose. Neutralization was then maintained by single daily administration of omeprazole (10 mEq ANC + 20 mg omeprazole) over the course of the study.

15 **Lack of Effect of omeprazole in prevention of meal-induced heartburn**

Decktor recently reported a single administration of omeprazole 10 or 20 mg failed to prevent meal-induced heartburn. Decktor, et al., *Am. J. Gastroenterol.* **93**: 1614, (1998). 385 subjects with a history of food-induced heartburn participated in a single-dose, parallel, blinded, randomized, placebo-controlled trial. 60 minutes prior to receiving a standardized heartburn-inducing meal (chili and soft drink), subjects received either placebo, 10 mg famotidine (Pepcid AC), omeprazole 10 mg or omeprazole 20 mg. Subjects rated their heartburn symptom severity on a VAS scale beginning immediately prior to the meal, and at 30 min. intervals for 3 ½ hr postprandially. Compared to placebo, neither dose of omeprazole significantly prevented or reduced postprandial heartburn; 54, 52 and 55% of subjects treated with placebo, 10 mg omeprazole or 20 mg omeprazole reported moderate-to-severe postprandial heartburn symptoms. In contrast, 34% of subjects treated with famotidine were heartburn free, and only 27% reported moderate to severe symptoms (consistent with previously published trials). 64% of subjects reported relief from 10 mg famotidine as good or excellent, compared to 40%, 42% and 47% treated with placebo, 10 mg omeprazole and 20 mg omeprazole, respectively ($p < 0.03$ vs. famotidine). Neither dose of omeprazole differed significantly from placebo for any efficacy parameter. This study showed a clear performance advantage for famotidine over omeprazole in prevention of meal-induced heartburn symptoms.

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The present invention is directed to the recognition that a 10 or 20 mg dosage of omeprazole and a preferred acid neutralizing capacity of a bicarbonate salt is/will be sufficient to induce relief of heartburn symptoms without requiring additional dosing of the bicarbonate salt.

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Study to prove effectiveness of a combination therapy in heartburn relief and prevention.

A suitable study involves administration of a provocative meal (chili, soft drink) to individuals who report suffering from meal-induced heartburn, and whose heartburn symptoms can be reproduced by the provocative meal and responds to antacid/acid neutralization treatment. Following development of heartburn, usually within 30 – 60 min of eating the meal, the combination of omeprazole and bicarbonate is administered in a randomized, blinded manner (10 – 20 mL containing 10 – 20 mEq (ANC) bicarbonate and 10 – 20 mg omeprazole). Control treatments include bicarbonate alone, omeprazole alone, and placebo. Both the combination and bicarbonate treatments will provide rapid relief of heartburn symptoms, while lesser relief is attained with omeprazole and placebo (no difference between the latter treatments in degree of relief). A second heartburn provoking meal is then consumed at least 4 hours after the first meal, but no further treatments are administered. Those subjects who receive omeprazole-containing treatments after the initial meal experience a reduction in heartburn symptoms to the second meal. Subjects who receive antacid alone (bicarbonate) or placebo treatment with the first meal are expected to have fully recurrent symptoms to the later meal. Hence, the combination of bicarbonate + omeprazole provides for a rapid onset and a prolonged duration of heartburn relief.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples

herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A method of treating or preventing heartburn symptoms in a human in need thereof, which method comprises administering to said human a pharmaceutical composition comprising an effective amount of a proton pump inhibitor and an effective acid neutralizing amount of an alkali metal bicarbonate salt.

2. The method according to Claim 1 wherein the proton pump inhibitor is omeprazole, lansoprazole, pantoprazole, perprazole, or rabeprazole, or salts, isomers, enantiomers or derviations thereof.

3. The method according to Claim 2 wherein the proton pump inhibitor is omeprazole.

4. The method according to Claim 3 wherein the dose of omeprazole is from about 10 to about 20mg.

5. The method according to any one of Claims 1 to 4 wherein the bicarbonate is sodium or potassium bicarbonate or a mixture thereof.

6. The method according to Claim 5 wherein the bicarbonate is sodium bicarbonate.

7. The method according to Claim 6 wherein the bicarbonate is administered in an ANC amount of about 18 to 40mEq.

8. The method according to Claim 1 wherein the proton pump inhibitor and alkali metal bicarbonate salt are administered in a solid unit dosage form.

8. The method according to Claim 8 wherein the dosage form is a compressed tablet.

9. The method according to Claim 8 wherein the dosage form is a capsule.

10. The method according to Claim 7 wherein the proton pump inhibitor is omeprazole and in a dosage range of from about 10 to about 20 mg.

11. The method according to Claim 1, wherein the pharmaceutical composition is a single unit dosage form administered in a volume of between approximately 10 ml and 20 ml of an aqueous solution.

- 5 12 The method according to Claim 11 wherein the dosage form is a sachet administered with water.

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"HEARTBURN TREATMENT"

the specification of which (check one)

☐ is attached hereto.

☒ was filed on **12 July 00** as Serial No. **PCT/US00/18896**
and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
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I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/143,407	12 July 1999

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status
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I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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